Research and Reviews: Research Journal of Oncology

Extended Abstract
Vol. 3, Iss. 3
2019

Cancer Science 2018: Therapeutic ultrasound-mediated delivery of the gene encoding for the tumor suppressor, Sef, into prostate tumors suppressed tumor growth and revealed Sef potent antiangiogenic activity - Prof. Dina Ron - Professor, Biology Department Technion, Israel

Dina Ron
Biology Department Technion, Israel

Carcinomas account for over 80% of all human cancer types with no effective therapies. The tumor suppressor Sef [similar expression to fibroblast growth factors (FGF)] is expressed in all the human epithelial tissues and is down-regulated in all the carcinoma types that have been examined so far in a manner that correlates with tumor aggressiveness. We examined the therapeutic potential of restoring the expression of the hSef-b isoform in a prostate carcinoma model. In our in vitro studies, hSef-b inhibited the proliferation of TRAMP C2 cells and attenuated the activation of ERK/MAPK as well as the master transcription factor NF-κB in response to FGF and IL-1/TNF, respectively. Both FGF and NF-κB are strongly implicated in prostate carcinoma progression. Next, the hSef-b, gene was delivered using therapeutic ultrasound (TUS) to pre-established prostate tumors in vivo. Tumors were injected with a bicistronic vector co-expressing hSef-b with eGFP to serve as a reporter for transfection rates, and treated with TUS. Transfection efficiency of plasmid co-expressing hSef-b/eGFP into TRAMP C2 tumors following a single TUS application was 14.7± 2.5%. Repeated TUS treatments with hSef-b plasmid, significantly suppressed prostate tumor growth (60%) through inhibition of cell proliferation (60%), and also reduced blood vessel density (56%). In addition, the levels of the promitogenic and proangiogenic factor, FGF2, were significantly reduced following repeated TUS treatments with hSef-b plasmid. Collectively, our results strongly suggest that hSef-b acts in a cell autonomous as well as in a paracrine manner and further revealed the efficacy of non-viral, TUS-based hSef-b gene delivery approach for the treatment of prostate cancer tumors, and possibly other carcinomas where Sef is downregulated. Moreover, using this approach, we discovered that hSef-b is also furnished with the capacity to inhibit tumor angiogenesis.

The human FGF gene family consists of at least 23 different genes encoding related polypeptides. FGFs are expressed in almost all tissues and play important roles in a variety of normal and pathological processes, including development, wound healing and neoplastic transformation. The FGFs are mitogenic for many cell types, both epithelial and mesenchymal. Some FGFs, like FGF2, have potent angiogenic activity and have been implicated as promoters of tumor angiogenesis. FGFs have also been shown to increase the motility and invasiveness of a variety of cell types. Finally, it has been shown that FGFs can inhibit cell death in the appropriate context. Thus FGFs have a broad range of biological activities that can play an important role in tumorigenesis.

FGFs interact with a family of four distinct, high-affinity tyrosine kinase receptors, designated FGFR-1 to -4 (Johnson & Williams 1993). The receptors consist of an extracellular portion containing three immunoglobulin-like domains and an intracellular tyrosine kinase domain and have variable affinities for the different FGFs. In addition, FGFRs-1 to -3 all undergo an alternative splicing event in which two alternative exons (IIIb and IIIc) can be used to encode the carboxy terminal portion of the third immunoglobulin-like loop, which results in receptor isoforms with dramatically altered binding specificity. The IIIa alternatively spliced isoform is secreted. A variety of other alternative splicing events have been described, including alternative splicing that results in loss of the first extracellular immunoglobulin-like domain.

This work is partly presented at the Event on International Conference on Cancer Science, July 23-24, 2018 held at Amsterdam, Netherlands